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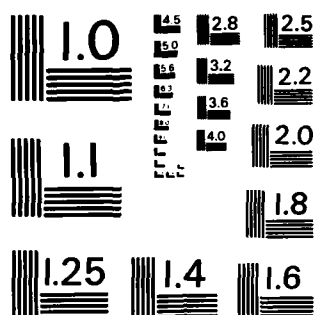
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COMPARATIVE HYPNOTIC EFFECTS OF FLURAZEPAM, TRIAZOLAM, AND  
PLACEBO: A REANALYSIS\*

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## SUMMARY

A recent study examined the effects of 30 mg flurazepam, 0.5 mg triazolam, and a placebo in 21 chronic insomniacs who were studied over 59 nights in a parallel groups design. This reanalysis made additional comparisons in addition to reevaluating those previously reported to gain new insights as to the action of these two hypnotics. Upon reanalysis the between- and within-group results indicate similar efficacy for improvement in sleep, especially during the early weeks of treatment. The placebo had no consistent impact on any of the sleep variables and showed greater night to night variability. Triazolam patients showed a marked increase in sleep latency during the first two withdrawal nights. For these patients, however, there was no rebound in awake time after sleep onset. The flurazepam patients' withdrawal sleep was not statistically different from the placebo group or from their own baseline. In contrast to triazolam patients, flurazepam patients' poor sleep, when present, occurred throughout the withdrawal period with no clustering on one or more nights. There was no clear relationship between plasma N-desalkylflurazepam level during treatment or elimination rate during withdrawal to sleep measures.

These findings are consistent with reports which state that after chronic benzodiazepine use, hypnotic patients may experience one or two nights of poor sleep when treatment is discontinued. For short half-life drugs poorer sleep, if present, occurs on the first withdrawal nights, but for hypnotics with long half-lives poor sleep, if present, may occur any time during the following two-week period. Reanalysis of the pattern of daytime results indicated that performance of flurazepam patients was most affected.



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## INTRODUCTION

Mitler et al.<sup>1</sup> reported the effects of 30 mg flurazepam, 0.5 mg triazolam, and a placebo in 21 chronic insomniacs (seven in each group, mean age  $43 \pm 12.7$  years) who were studied over 59 nights in a parallel groups design. There were three baseline nights, nine placebo nights, 37 treatment nights, and 10 withdrawal nights. On 32 of these nights, all-night EEG recordings were obtained. Blood samples for plasma analysis and daytime performance data were obtained on medication day 3 and on five occasions thereafter at weekly intervals. The reader is referred to Mitler et al.<sup>1</sup> for a complete description of the procedure.

The dollar cost plus the extensive commitment of laboratory time and personnel were such that the likelihood of a replication of this study is unlikely. It is, therefore, important that maximum utilization be made of these data. This reanalysis made additional comparisons in addition to reevaluating those previously reported to gain new insights as to the action of these two hypnotics. Though this reanalysis was completed before the Kales<sup>2</sup> commentary on the Mitler et al.<sup>1</sup> paper was published, the key issues raised by Kales are addressed here.

Statistical Analysis: The designers of this study approached forthrightly a major problem of chronic drug studies, i.e., determining the effects of being in the study over such a long period of time. The inclusion of a placebo group provided a direct answer to this question. The design also lent itself to a straight forward analysis of variance approach to ascertain whether there were treatment group differences and whether there were differences over the course of the study (weeks) and whether these time differences were consistent over groups for the nine weeks (weeks X treatment group interaction).

Normally, when there are no significant group or weeks main effects or significant interactions in a design such as this, the nonsignificant ANOVAs should not be followed by between- or within-group analysis. In a parallel groups design, the placebo group provides the control for changes over time, practice effects, and other procedural effects. When the nonsignificance of the ANOVAs is ignored and

within-group comparisons are made, the control for effects over time is eliminated. Significant within-group findings could be due to changes over time rather than to treatment effects. Changes over time are of particular concern in the analysis of daytime performance where practice effects could be present. Mitler et al.<sup>1</sup> planned a priori to do both between- and within-group comparisons, but because they expected that the small number of subjects in each group would lead to high between subjects variability which would preclude obtaining significant between-groups effects in key sleep parameters, they focused on the within-group analysis.

In this reanalysis of the data, post hoc between- and within-group comparisons of variables were made only when ANOVA main effects or interactions were significant ( $p < .05$ ). In contrast to the original analysis which did a separate ANOVA for each study phase, i.e., baseline, treatment, and withdrawal, the omnibus ANOVA in this reanalysis included all study nights within weeks and all nine weeks of the study, permitting an examination of effects of weeks as well as the weeks X treatment group interaction over the total study period.

Sleep Variables: In an effort to insure cooperation in such a demanding study and to more closely approximate the "real world" of insomniacs, the study designers allowed each patient to determine his/her own bedtime each night. This flexibility led to great between and within patient variability of time in bed (TBT) and, consequently, in total sleep time (TST). The night to night variability within patients can lead to questionable conclusions if TST is used as the dependent variable. Without detailed information as to the reason(s) for changes in TBT, it is difficult to explain changes in TST in terms of any specific treatment. For example, two of the flurazepam patients had markedly reduced TST during withdrawal. They also had markedly reduced TBT on these two nights. Both patients awoke early. For one patient this was not uncommon as early awakening had occurred during treatment and pretreatment. The spontaneous awakening one hour before the usual awakening time was uncommon for the second patient, and no explanation is available. However, the sleep efficiency for these two patients was consistent with their sleep efficiency on other treatment and withdrawal nights.

Sleep efficiency ( $[(TST \div TBT) \times 100]$ ) is more often reported than TST in studies

in which bedtime varies. In this reanalysis, sleep efficiency was used as the measure of overall quality of sleep. This choice provides additional perspective on the results of the analyses of Mitler et al.<sup>1</sup> because the influence of TBT is held constant. In addition, sleep latency and time awake after sleep onset and before final awakening (awake time after sleep onset) were also reanalyzed. The focus of this reanalysis was on the sleep quality data and, in particular, sleep during the withdrawal period.

In addition to the concern over failure to control total bedtime, Kales<sup>2</sup> also criticized Mitler et al.<sup>1</sup> for failing to "provide any adaptation to the sleep laboratory for each group [week] of nights analyzed". In the reanalysis, we examined adaptation. We also looked more closely at the placebo effect, and all within-group treatment comparisons were made using the pretreatment placebo values and not baseline week values, another issue raised by Kales<sup>2</sup>. However, sleep during withdrawal was compared to baseline week values (preplacebo) as the best indicator of pretreatment sleep for evaluation of rebound insomnia. For patients taking flurazepam, the relationship between sleep during treatment and withdrawal and plasma levels of N-desalkylflurazepam was also reexamined. Only a broad look at the pattern of daytime performance among the three groups is reported.

## RESULTS

### Adaptation Effect

First night effect was examined by ANOVA for each week separately, in which the main effects were treatment group, nights, and nights X treatment group interaction. When the F value for nights was significant, the three nights in that week were examined to see which night was significantly different. There were no significant nights X treatment group effects for any week for the three sleep measures: sleep efficiency, sleep latency and awake time after sleep onset.

Sleep Efficiency: There was a significant F for sleep efficiency ( $F_{(2,36)}=4.86$ ,  $p<.01$ ) during the baseline week. Inspection of individual nights indicated a clear first night effect. The mean sleep efficiency for baseline night 1 was  $79.3 \pm$



24.32, and for baseline nights 2 and 3 the respective means and standard deviations were  $86.4 \pm 12.23$  and  $85.94 \pm 7.61$ . However, there was no significant effect for nights for any other week during the remainder of the study. In some weeks, sleep efficiency was highest on the first night.

Sleep Latency: Though sleep latency was longer on baseline night 1, the F value was not significant. The only significant nights effect was associated with the second treatment week ( $F_{(2,36)}=3.26, p<.05$ ). The sleep latency for the first night of this week was  $15.8 \pm 11.25$  while that for the second and third nights were  $10.30 \pm 9.11$  and  $10.78 \pm 7.44$ , respectively.

Awake Time After Sleep Onset: There were no significant nights effects in any week. The p value for the nights factor was .09 for the baseline week. Awake time after sleep onset was higher on the first baseline night.

In summary, the only clear sign of an adaptation problem was that seen on the first night in the laboratory which influenced the baseline mean values (See Figures 1, 2, and 3).

#### Sleep Efficiency

ANOVA: In Figure 1 are the mean sleep efficiency values for each group for each of the recorded study nights. Five study nights (all Friday nights) preceeding the Saturday daytime testing and blood sample drawings were not included in the Mitler et al.<sup>1</sup> original analysis and were also not included in the reanalysis ANOVAs. Inspection of these Friday nights indicated that sleep quality was similar to other nights of that week. As three nights were reported for each week, the reader can easily separate the nights into weeks by dividing the night by number three. The three placebo nights analyzed were the 7th, 8th, and 9th nights of placebo ingestion.

The overall ANOVA indicated a significant weeks effect ( $F_{(8,144)}=6.10, p<.0002$ ) and a significant weeks X treatment group interaction ( $F_{(16,144)}=2.93, p<.007$ ). Because repeated measures were analyzed, the conservative Greenhouse-Geisser test was used for all p values.

Figure 1  
Mean EEG sleep efficiency on laboratory sleep nights during withdrawal baseline (B), placebo (P), treatment (T), and withdrawal (W). For all figures, to determine study week, divide the night number by three.

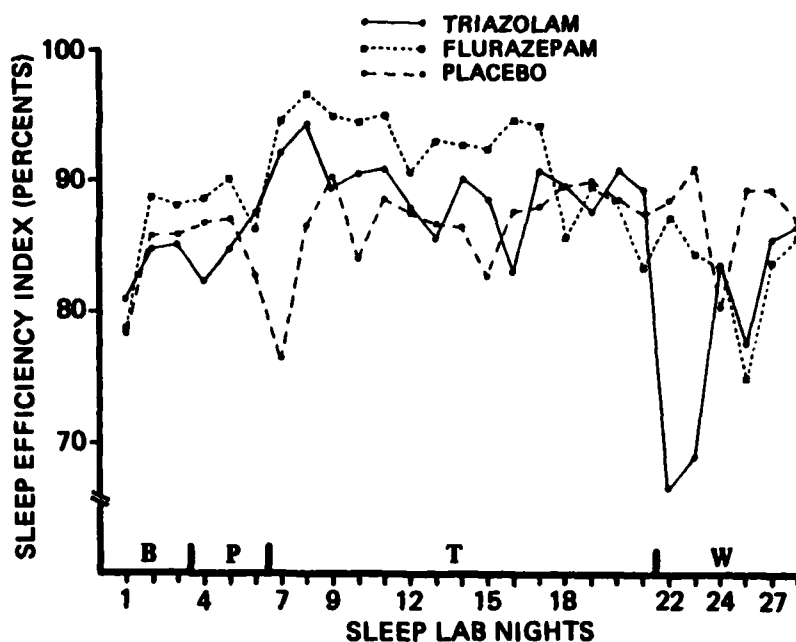
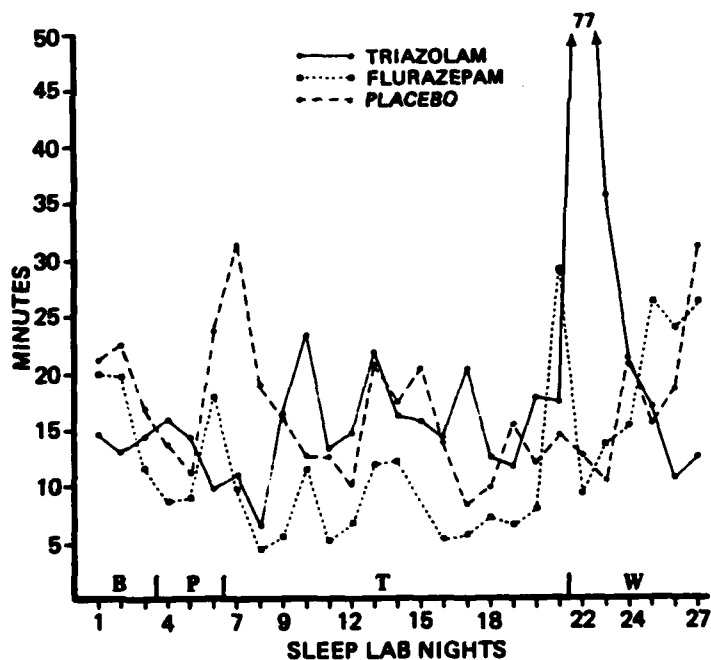


Figure 2  
Mean EEG sleep latency in minutes on sleep laboratory nights during baseline (B), placebo (P), treatment (T), and withdrawal (W).



**Between-Groups Comparisons:** Pairwise contrasts using difference scores (treatment week minus pretreatment placebo week) indicated that both drug groups had significantly higher sleep efficiency than the placebo group during the first two weeks of treatment (see Table 1). One-tailed p values were used for all drug versus placebo contrast. Mitler et al.<sup>1</sup> used only two-tailed tests throughout their report. We used two-tailed tests for drug group contrasts. Comparisons of difference scores for the two drug groups during treatment yielded no significant differences for sleep efficiency, sleep latency or awake time after sleep onset. Between-groups treatment differences for drug groups will not be reported further.

Table 1  
Means and Standard Deviations for Sleep Efficiency

Group		Weeks								
		W	P	T1	T2	T3	T4	T5	WM1	WM2
TRZ	$\bar{X}$	83.59	84.86	91.96 <sup>1,2</sup>	89.60 <sup>1,2</sup>	88.21	87.82	89.42	72.97 <sup>1,3</sup>	83.35
	S.D.	8.88	9.25	3.98	5.07	3.76	5.20	5.73	15.46	10.24
FLZ	$\bar{X}$	85.16	88.29	95.46 <sup>1,2</sup>	93.54 <sup>1,2</sup>	92.71 <sup>2</sup>	91.45	87.26	85.08	81.34
	S.D.	7.59	6.50	4.23	4.91	4.27	4.19	14.95	8.27	11.42
PLA	$\bar{X}$	83.30	85.40	84.30	86.79	85.14	88.59	88.67	86.63	88.49
	S.D.	13.56	13.53	15.54	9.63	13.40	9.65	6.45	15.08	7.94

For tables 1, 2, & 3; TRZ = Triazolam, FLZ = Flurazepam and PLA = Placebo. One-tailed p values are cited for drug group comparisons with placebo group and for within drug group treatment weeks (T1-5) comparisons with pretreatment placebo week (P). All other comparisons are two-tailed. Significant =  $p < .05$ .

- <sup>1</sup> = Significant from placebo group
- <sup>2</sup> = Significant from pretreatment placebo week
- <sup>3</sup> = Significant from pretreatment baseline week

As the data in Figure 1 indicate, the major treatment group differences were found in the first withdrawal week data and in particular, on the first two withdrawal nights. Pairwise comparisons were done for these withdrawal nights. For these two nights, mean sleep efficiency for triazolam was  $67.8 \pm 19.04$ ; for flurazepam,  $85.8 \pm 9.39$ ; and for placebo  $89.9 \pm 7.76$ . Triazolam sleep efficiency was significantly lower than both flurazepam and placebo ( $t_{(12)}=2.24$ ,  $p < .05$ , and  $t_{(12)}=2.84$ ,  $p < .02$  respectively). Flurazepam and placebo groups did not differ significantly. There were no significant pairwise differences among the three groups for any other withdrawal night.

The low night 7 sleep efficiency for the placebo group was due to the very low value of 8% for a single patient. On night 21, one flurazepam patient's sleep efficiency of 29% lowered the mean and increased the standard deviation values. In general, the placebo patients showed greater night to night variability during treatment (Table 1).

Within-Group Comparisons: For the 21 patients, baseline week sleep efficiency was  $84.0 \pm 9.84$  and placebo week sleep efficiency was  $86.2 \pm 9.78$ . This increase during placebo intake was significant ( $t_{(20)}=2.11$ ,  $p<.05$ ). There was also a decrease in sleep latency during placebo pretreatment (baseline  $17.2 \pm 14.01$ , placebo  $13.8 \pm 10.43$  minutes) but the p value was .09. The decrease in awake time during baseline ( $45.7 \pm 37.45$ ) to that during placebo pretreatment ( $41.6 \pm 35.83$ ), was nonsignificant. The within-group analysis compared each treatment week value against the pretreatment placebo week values. As noted earlier, withdrawal sleep was compared to baseline sleep to determine rebound effects, i.e., whether sleep was poorer than that at onset of the study.

The means, standard deviations and significance of comparisons for the week by week data are listed in Table 1. As an increase in sleep quality was predicted during treatment for both hypnotics, the p values used for treatment comparisons with pretreatment were one-tailed. For all withdrawal-baseline and for placebo within-group comparisons, the p value was two-tailed.

**Triazolam:** Sleep efficiency was significantly higher than placebo week values during the first and second treatment weeks. Compared to baseline, during the first withdrawal week<sup>o</sup> there was a significant reduction in sleep efficiency but sleep efficiency returned to baseline during the second withdrawal week. Six of the seven patients' sleep efficiency during withdrawal week 1 was lower than baseline. For the first two withdrawal nights, the difference from placebo was significant.

**Flurazepam:** When treatment weeks were compared to placebo, sleep efficiency was significantly improved during the first three weeks of treatment. Withdrawal sleep was not significantly different from baseline. The lower value during the second

withdrawal week was due to the lower values of two patients. Three of the seven patients had a higher sleep efficiency during withdrawal week 2 than during baseline.

Placebo: There were no statistically significant differences for any within-group comparison for the patients receiving a placebo.

In summary, both drugs significantly increased sleep efficiency during the first two treatment weeks compared to placebo, but the most striking between-groups differences occurred during the first withdrawal week. Compared to their own pretreatment values, both hypnotics were effective in improving sleep efficiency. The placebo was ineffective. The improvement over their placebo week values was significant only for the first two weeks of treatment for triazolam and for the first three treatment weeks for flurazepam. Only triazolam showed a significant impairment in sleep efficiency during withdrawal when compared to baseline. Sleep efficiency, however, was significantly lower only during the first two withdrawal nights of the first week.

Figure 3  
Mean EEG awake time after  
sleep onset and before final  
awakening on sleep laboratory  
nights during baseline (B),  
placebo (P), treatment (T),  
and withdrawal (W).

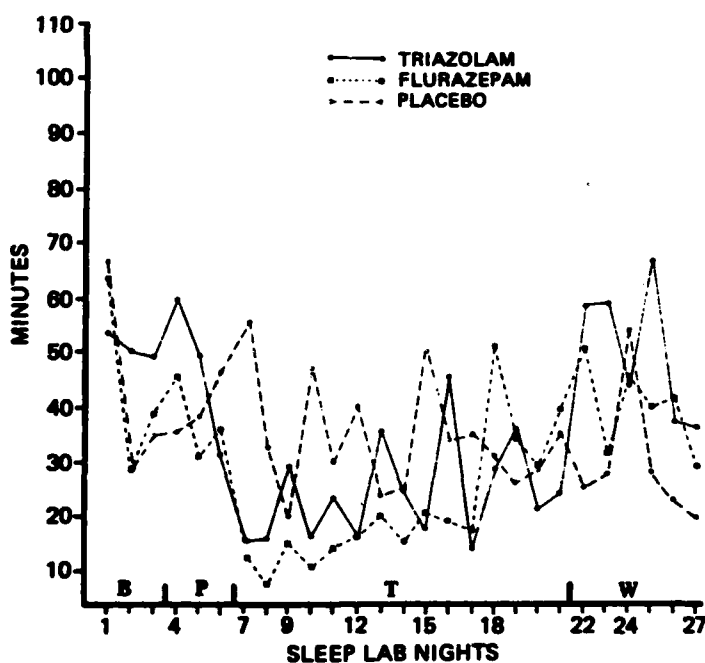
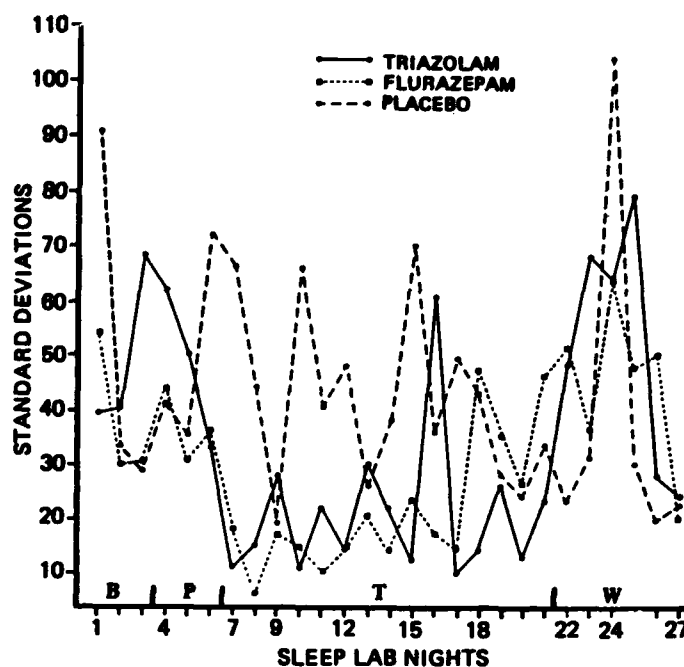


Figure 4  
Variability of awake time  
(minutes) after sleep onset  
and before final awakening  
on sleep laboratory nights  
during baseline (B), placebo  
(P), treatment (T), and with-  
drawal (W).



#### Further Evaluation of Rebound

In their paper, Mitler et al.<sup>1</sup> presented the hypothesis that since the elimination rate of a long-acting metabolite varies from patient to patient, any rebound would not necessarily occur on the same night for each patient. To examine this possibility, sleep loss was computed by dividing the shortest TST night during withdrawal by the lowest TST night during baseline, subtracting from one and expressed as a percent (see their Figures 3 and 4). They reported that six of the seven patients taking flurazepam had "markedly poorer" sleep during withdrawal.

As we noted earlier, two flurazepam patients had markedly shorter TBT due to early spontaneous awakenings during this period. Here, we compared, for flurazepam patients, their lowest sleep efficiency night during withdrawal directly with their lowest sleep efficiency night during baseline. Using sleep efficiency, there was no significant difference between the two periods, though the differences were in the expected direction. Baseline mean of lowest sleep efficiency was  $77.4 \pm 10.55$ ,

withdrawal was  $61.7 \pm 24.6$ , ( $t_{(6)} = 2.23$ ,  $p$  between .05 and .10). In a patient by patient inspection, however, five of the patients had a sleep efficiency on one night below 80% and four of these were below 60% on one night during withdrawal. The other two patients' sleep efficiencies were 83% and 92% and were within one percent of baseline values. Four patients had sleep efficiencies below 80% on one night during baseline but none had a sleep efficiency lower than 60% on any baseline night. The night of lowest sleep efficiency varied from patient to patient with one or more low values on all withdrawal nights except night 1. Four lowest values occurred on withdrawal night 3 and four on withdrawal night 8. The worsening of sleep measured by TST during withdrawal, reported by Mitler et al<sup>1</sup>, was also seen when sleep efficiency was used, but to a lesser degree.

Kales criticized Mitler et al.<sup>1</sup> for not conducting a similar analysis on the placebo group. We did such an analysis. Lowest sleep efficiency within-group comparisons for the patients receiving placebo indicated no significant withdrawal problems. During withdrawal, the mean of the seven nights with lowest sleep efficiency was 75% and the mean during baseline was 80%. Only four of the patients had their poorest night of sleep during withdrawal.

#### Sleep Latency

ANOVA: A significant weeks effect ( $F_{(8,144)}=2.97$ ,  $p<.01$ ) and a weeks X treatment group interaction ( $F_{(16,144)}=2.79$ ,  $p<.005$ ) were found. As indicated in Figure 2, the weeks X treatment group interaction was due to the marked increase in sleep latency of the triazolam patients during the first withdrawal week. This elevation, however, was present only for the first two withdrawal nights (see Figure 2).

Between-Groups Comparisons: Pairwise comparisons indicated no significant between-groups differences except during the first withdrawal week. The sleep latency of patients receiving flurazepam was the lowest of the three groups during most treatment weeks, but the difference approached significance, when compared to the placebo group, only during treatment week 1 ( $p<.06$ ). During withdrawal week 1, the mean sleep latency for triazolam patients was  $44.5 \pm 23.3$ , for flurazepam  $12.6 \pm$

9.80, and for placebo  $16.3 \pm 10.48$ . The  $t_{(12)}$  value for the comparison of triazolam with flurazepam was 3.34,  $p < .006$ , and for placebo was 2.92,  $p < .01$ . The difference between flurazepam and placebo groups was not significant. Pairwise night comparisons during the first withdrawal week indicated significant differences only for the first two nights (See Figure 2).

#### Within-Group Comparisons:

Triazolam: Sleep latency was not significantly lower during any treatment week when compared to placebo week (Figure 2, Table 2). But latency was significantly higher during the first withdrawal week than that for baseline week ( $t_{(6)} = 3.87$ ,  $p < .008$ ). But only mean latencies for nights 1 and 2 were significantly higher than baseline means. Withdrawal week 2 values were not significantly different from baseline.

Table 2  
Means and Standard Deviations for Sleep Latency

Group		Weeks								
		B	P	T1	T2	T3	T4	T5	WW1	WW2
TRZ	$\bar{X}$	14.05	13.36	11.26	17.00	17.88	15.68	15.61	44.49 <sup>3,4</sup>	13.34
	S.D.	6.99	7.96	8.02	13.31	11.42	12.69	17.12	23.31	8.02
FLZ	$\bar{X}$	17.10	11.78	6.53 <sup>1,2</sup>	7.72	10.82	6.01	14.42	12.60	25.47
	S.D.	21.91	11.51	9.30	4.85	10.96	3.26	24.84	9.80	29.37
PLA	$\bar{X}$	20.43	16.19	22.07	12.11 <sup>1</sup>	19.49	10.62 <sup>1</sup>	13.87	16.32	21.55
	S.D.	10.09	12.47	25.89	5.67	11.12	8.00	11.07	10.48	12.62

<sup>1</sup> = Comparison with placebo group;  $p = .06$

<sup>2</sup> = Significant from pretreatment placebo week

<sup>3</sup> = Significant from pretreatment baseline week

<sup>4</sup> = Significant from flurazepam, and placebo groups

Flurazepam: When treatment weeks were contrasted with placebo week, the decrease during the first treatment week was significant ( $t_{(6)} = 3.44$ ,  $p < .01$ ) but no other comparison was significant.

Comparison of the longest sleep latency during withdrawal with the longest during baseline for each patient also revealed no significant difference though the mean latency during withdrawal,  $40.4 \pm 45.56$ , was higher than during baseline,  $23.2 \pm 28.87$  minutes. Five of the patients had longer latencies during withdrawal. As



with sleep percent, the longer latencies did not occur on a single withdrawal night or on adjacent nights.

**Placebo:** For placebo patients, sleep latency during treatment was similar to pretreatment. Withdrawal latencies also did not differ significantly when compared to baseline.

Examination of the longest latencies for each placebo patient during withdrawal and baseline revealed no significant differences: withdrawal mean,  $42.7 \pm 31.16$ , baseline mean,  $35.4 \pm 19.06$ . Three patients had their longest latency during withdrawal; one was unchanged.

In summary, sleep onset insomnia was not a major problem for these patients and the hypnotics had minimal effect. The major contrast between the two drugs was the marked increase in sleep latency on the first two withdrawal nights for patients withdrawing from triazolam. Placebo effect on sleep latency was variable from week to week.

#### Awake Time After Sleep Onset and Before Final Awakening

**ANOVA:** The data in Figure 3 indicate that maintaining sleep was a major problem for these patients, and the data in Figure 4 indicate that the variability differed among the three groups and from night to night within groups. During treatment, the placebo group continued to show great night to night variability, but variability decreased for the two drug groups, especially during the first two weeks of treatment. The higher mean scores for the triazolam group on nights 13 and 16 were due to high awake values for a single, and different patient each night. With such a large difference among groups in variability, the power of F tests may be curtailed. The F value for weeks, however, was significant ( $F_{(8,144)}=4.32, p<.004$ ). The weeks X treatment group interaction was not significant.

**Between-Groups Comparisons:** Both drug groups showed similar mean changes from placebo baseline (see Table 3), but the variability was higher for the flurazepam patients. For example, during treatment week 1 the mean change from placebo week in

awake time was 26 minutes for both groups, but the standard deviation was 26.2 for triazolam and 33.3 minutes for the flurazepam group. The triazolam patients' mean change scores were significantly lower than the placebo mean change ( $t_{(12)}=2.02$ ,  $p<.03$  and  $t_{(12)}=2.16$ ,  $p<.025$ ), weeks 1 and 2 respectively. Because of the higher variability, the p values for the comparisons between flurazepam and placebo groups were .07 for both weeks 1 and 2.

Table 3  
Means and Standard Deviations for Wake Time After Sleep Onset and Before Final Awakening

Group		B	P	Weeks					WW1	WW2
				T1	T2	T3	T4	T5		
TRZ	$\bar{X}$	50.47	46.58	20.40 <sup>1,2</sup>	18.90 <sup>1,2</sup>	26.11 <sup>2</sup>	29.07 <sup>2</sup>	27.35	53.47	46.87
	S.D.	40.23	31.40	15.55	14.77	10.82	23.04	16.93	47.45	33.44
FLZ	$\bar{X}$	42.96	37.99	11.66 <sup>1,2</sup>	13.60 <sup>1,2</sup>	18.95	29.65	34.45	42.73	37.77
	S.D.	30.03	35.55	12.36	8.49	17.98	17.36	34.66	29.97	27.88
PLA	$\bar{X}$	43.53	40.32	36.32	38.96	32.87 <sup>1</sup>	33.54	29.90	35.65	23.59
	S.D.	45.94	44.69	36.63	35.38	40.60	40.64	25.12	47.29	22.94

<sup>1</sup> = Significant from placebo group. For flurazepam, p values are .07

<sup>2</sup> = Significant from pretreatment placebo week

In contrast to sleep efficiency and sleep latency, there were no significant between-groups differences during withdrawal.

#### Within-Group Comparisons:

Triazolam: When compared to placebo, treatment weeks 1, 2, 3, and 4 were significantly lower. The respective  $t_{(6)}$  values were: 2.86,  $p<.015$ ; 3.03,  $p<.01$ ; 2.00,  $p<.045$ ; and 1.91,  $p<.052$ . Withdrawal values were not significantly different from baseline week.

Flurazepam: Compared to placebo, treatment weeks 1 and 2 differed significantly ( $t_{(6)}=2.09$ ,  $p<.05$ , and  $t_{(6)}=1.98$ ,  $p<.05$ ). There were no significant differences when withdrawal was compared to baseline.

When we compared the withdrawal nights with longest awake time for each patient with the comparable baseline nights, we found the flurazepam patients had higher, but, not significantly higher, awake time during withdrawal. The withdrawal mean was 101

$\pm 54.0$  minutes and during baseline the mean was  $72 \pm 49.8$  minutes. Four patients awake time was longer during withdrawal than baseline. Like sleep efficiency and sleep latency the increased awake time occurred on different nights for different patients over several withdrawal nights.

Placebo: These patients' awake time during treatment did not vary significantly from placebo week nor was withdrawal awake time significantly different from baseline.

In summary, in contrast to both sleep efficiency and sleep latency, there were no significant between-groups differences during withdrawal. The hypnotics significantly decreased awake time after sleep onset when compared to placebo week pretreatment values. Triazolam was effective over placebo week during four weeks of treatment. The flurazepam effect was significant on the first two weeks of treatment. The placebo effect was highly variable.

#### Other Measures of Awake Time

This reanalysis of the data indicated, as did the analysis by Mitler et al.<sup>1</sup>, that there were no significant treatment group differences or weeks X treatment group interaction for wake time after final awakening. Though not reported by Mitler et al.<sup>1</sup>, the original analysis found no significant group differences in awakenings during the last third of the night during treatment. These negative findings are of interest because of the published report of more frequent early morning awakenings in patients taking hypnotics with a short half-life (Kales et al.<sup>3</sup>).

#### Relationship of Sleep to Plasma levels

Since there were no measurable amounts of triazolam in plasma, this analysis was confined to data from the flurazepam group. The pattern of build-up and withdrawal of N-desalkylflurazepam has been detailed by Mitler et al.<sup>1</sup> and by Johnson et al.<sup>4</sup>. In their analysis, Mitler et al.<sup>1</sup> were concerned with the relationship between changes in plasma levels and changes in sleep during withdrawal and presented a scatterplot depicting this relationship (their Figure 4). In this reanalysis,

N-desalkylflurazepam plasma levels were related to sleep efficiency during treatment and withdrawal, and to changes from treatment in both plasma levels and sleep during withdrawal. Because of the small N and the extreme values of some patients, rank order (rho) correlations were computed.

Treatment: There was no significant relationship between N-desalkylflurazepam plasma levels and sleep efficiency after one week of treatment,  $\rho = .11$ . For an N of seven,  $\rho$  must be  $\geq .71$  for significance. At the end of the third week, the lack of variability in sleep efficiency rendered a correlational analysis meaningless. All patients, except one, had a sleep efficiency higher than 95%. The exception was 89%. Plasma levels ranged from 100 to 208 ng/ml.

Withdrawal: Though there was no statistically significant group rebound effect for the flurazepam patients, there was marked patient variability in sleep quality during the withdrawal period. Thus, as did Mitler et al.<sup>1</sup>, we examined the rate of N-desalkylflurazepam elimination from patient to patient and whether this differential pattern of elimination was related to the sleep of each patient. The reanalysis found no significant rank order correlation whether the same methodology used by Mitler et al.<sup>1</sup> was used or when other comparisons were made. When the relationship between percent of N-desalkylflurazepam eliminated during the first week of withdrawal was related to change in sleep efficiency from last treatment week, the  $\rho$  correlation was  $-.03$ .

When the percent N-desalkylflurazepam eliminated from blood was correlated with the lowest sleep efficiency night during withdrawal, the  $\rho$  was  $.44$ . The lack of any relationship was clearly illustrated by the data which showed that the patient with an N-desalkylflurazepam plasma level of 29% of maximum level had a sleep efficiency of 98%. The patient who still had 88% of his maximal N-desalkylflurazepam had a sleep efficiency of 99%. The average sleep efficiency for the 3 patients who still had 60% of their maximal N-desalkylflurazepam was 78.3% and the mean sleep efficiency was 78.7% for those who had eliminated more than 60% of their maximal plasma N-desalkylflurazepam. There were likewise no significant  $\rho$  values for sleep latency or for awake time after sleep onset.

During withdrawal, plasma levels were measured only on the Saturday morning at the end of the first withdrawal week. The sleep on Friday night, before the morning blood sample, was examined. The rho correlation between sleep efficiency and next morning plasma level was .46. The average sleep efficiency for the 3 patients with the lowest plasma levels ( $\bar{X}$  = 55 ng/ml) and for the three with the highest levels ( $\bar{X}$  = 110 ng/ml) was 79% for both groups.

#### Daytime Performance

Mitler et al.<sup>1</sup> found no significant F values and reported no significant between-groups differences for any of the daytime measures, including the Multiple Sleep Latency Test (MSLT) and the five performance tests. As discussed earlier, because of possible practice effects, within-group comparisons were not appropriate when there were no significant F values. Certainly no inference as to differential drug effects can be made on the basis of such within-group comparisons. Thus, the most parsimonious conclusion from the published data is that there was no clear statistically significant drug-related decrement or improvement in the daytime measures.

The published results, however, suggested a drug-related pattern of change from baseline in daytime performance. The flurazepam patients appeared to be more affected than did the triazolam patients. To determine whether such a pattern existed, a simple comparison was made of the mean values reported for treatment weeks 1, 3 and 5 with the mean values for baseline. The results are presented in Table 4. In the table are the number of mean values for each week which were higher than baseline means even if the actual difference was small, i.e., there was no mean performance decrement. These values in Table 4 are mean baseline-treatment comparisons for the MSLT and the 5 performance tests, with two scores on the divided attention test plus the Stanford Sleepiness Scale, making a total of 8 comparisons for each week and 24 comparisons for each group. The other performance tasks were choice reaction time, digit symbol substitution, Wilkinson addition, and target pursuit.

Table 4  
Treatment versus Baseline Daytime Performance

Number of daytime performance mean values that indicated no performance decrement when compared to baseline means.

Group	Weeks			Total	Percent
	T1	T3	T5		
Flurazepam	4	2	4	10	41.7
Triazolam	8	7	7	22	91.7
Placebo	5	5	6	16	66.7

The data in Table 4 support the observation that there was a differential drug effect on daytime performance. In 92% of the comparisons, the triazolam patients' mean values were better than baseline means; for flurazepam the percent was 42 and for placebo, 67. Because these are mean data, statistical tests were not done.

#### DISCUSSION

Reanalysis of the Mitler et al.<sup>1</sup> data provided additional information to that previously published in four areas: (1) the placebo effect; (2) the relative difference in efficacy of the two hypnotics on the sleep measures; (3) the differences among the treatment groups during withdrawal; and (4) the relationship of plasma levels of N-desalkylflurazepam to sleep during treatment and withdrawal.

The Placebo Effect: One of the most interesting results of this study was the influence of the placebo over the time course of the study. It has long been known that sleep improves during a placebo baseline period, but this study offered the opportunity to follow patients receiving a placebo over eight weeks. Though sleep quality improved during the nine pretreatment placebo nights, sleep efficiency was the only sleep measure that significantly improved over "nonpill" baseline when all 21 patients were compared. The significant increase in sleep efficiency reflected the additive improvement in sleep latency and awake time after sleep onset, though neither of these alone showed a significant change. When sleep latency and awake time after sleep onset were examined, the placebo was most effective in reducing sleep latency. This effect was present even though sleep onset insomnia was not a

major problem for these patients. This finding is not surprising if one considers the psychological set established by taking a "pill" to induce sleep. When there is an awakening during the night, the set might not be as strong and it would not be unusual for some patients to assume the "pill" is not working.

Mitler et al.<sup>1</sup> reported improved TST in the placebo patients and felt this was due to longer TBT. TST may have increased on some nights, but the results from this reanalysis indicate that, for placebo patients, neither sleep efficiency, sleep latency, nor awake time after sleep onset significantly improved over the pretreatment nights. On some nights, sleep quality, as measured by our sleep variables, was improved but this improvement was not consistent. For all sleep measures, the night to night variability was higher for placebo patients than for patients receiving a hypnotic. This higher variability was particularly true for awake time after sleep onset. During withdrawal, the placebo patients' sleep, however, did not suffer from the withdrawal of a sedative-hypnotic.

It is obvious that week to week variability in the placebo group will be an important factor in whether drug-placebo group differences are statistically significant. While the use of a parallel placebo group design with insomniac subjects is a more stringent design for efficacy, it is the only design which controls for both the placebo effect and the effect of time. The consistency of change in sleep quality over the nights of a study may be as important a measure of drug effectiveness as is the amount of change.

#### Efficacy:

Between-groups comparisons indicated significant between-groups differences in sleep efficiency and awake time after sleep onset for the first two to three weeks of treatment. While flurazepam was relatively more effective in reducing sleep latency and triazolam was relatively more effective in reducing awake time after sleep onset, there were no significant differences in efficacy between the two drugs. It is clear that neither drug maintained efficacy over the five weeks of treatment. For sleep efficiency, after two weeks of treatment, neither drug was superior to placebo.

The within-group findings were generally consistent with those for between-groups, but the within-group differences were present for more weeks. Both hypnotics improved sleep efficiency over pretreatment placebo levels for the first weeks of treatment. This effect was present for two weeks on triazolam and three weeks on flurazepam.

Awake time after sleep onset and before final awakening was the major sleep problem for these patients. For patients receiving triazolam, the drug reduced awake time from their pretreatment placebo levels over 4 weeks of treatment. Flurazepam reduced awake time from pretreatment placebo for the first two treatment weeks. The higher placebo week awake time may have been a factor in the longer effectiveness of triazolam. In this study, however, once a triazolam patient went to sleep, he/she usually stayed asleep. There was no major problem with awakenings during the last third of the night as has previously been reported by Kales et al.<sup>3</sup>

Withdrawal: Going to sleep was a problem during the first two withdrawal nights for the patients who had been taking triazolam. In contrast, there was no rebound in awake time after sleep onset. The increase in sleep latency on the first withdrawal night was dramatic and, for most patients, persisted to the second withdrawal night. By the third withdrawal night sleep latency was similar to baseline. On withdrawal nights 1 and 2 these patients experienced a sleep problem that was not present for most of them during pretreatment.

The reasons for this increase in sleep latency on the first two withdrawal nights from triazolam are unclear. Plasma analysis revealed no build-up of triazolam in plasma, though Johnson et al.<sup>4</sup> reported that the drug-related increase in sleep spindle rate per minute remained elevated and delta count remained low during the first withdrawal week. The clear association of the increased sleep latency with cessation of drug intake strongly suggests a withdrawal response. It is also of interest that there have been reports of lengthened sleep onset time on the MSLT, and some have stated that this reflected rebound anxiety related to withdrawal.<sup>5,6</sup> The results of this reanalysis suggest that efforts should be made to ascertain whether there is a physiological state during the day during treatment similar to



that seen at night upon withdrawal. The importance of dose levels should also be examined. It should also be noted that even if the increased daytime arousal level during treatment were a withdrawal response, if not excessive, this effect could be a positive benefit. The infrequent complaints of next day drowsiness and minimal performance decrement in the triazolam patients suggest that the increased arousal level is beneficial.

Though the sleep quality of most patients taking flurazepam was poorer on one or more nights during withdrawal than during baseline and poorer than that for placebo patients, there were no between- or within-group statistically significant differences for any sleep measure. Flurazepam patients also showed a different withdrawal pattern from that seen in patients withdrawing from triazolam. There was no consistent impairment in either sleep latency or awake time after sleep onset. Also, in contrast to triazolam, nights of poor sleep were spread over all the withdrawal nights. As a group, however, sleep efficiency was lower during the second withdrawal week. Oswald et al.<sup>6</sup> have reported that a period of poor sleep may be expected for as long as two weeks following 24 weeks of nightly ingestion of nitrazepam, 5 mg. Poor sleep during withdrawal after 24 weeks of lormetazepam, 2 mg, ingestion occurred during the first week with a peak on the second withdrawal night. The half-life of lormetazepam is 10 hours while that for nitrazepam is 30. Kales et al.<sup>7,8</sup> have reported on the potential for rebound insomnia immediately upon discontinuation of hypnotics with a short half-life. But Pegram et al.<sup>9</sup> found no rebound insomnia upon discontinuation of 0.5 mg triazolam after three weeks of use, and Spinweber and Johnson<sup>10</sup> reported no increase in sleep latency above baseline upon discontinuation of triazolam (0.5 mg) after six nights of use.

In contrast to both drug groups, the placebo patients continued to sleep as well (or as poorly) during withdrawal as they had on other nights.

Relationship to Plasma Levels: Mitler et al.<sup>1</sup> hypothesized that the pattern of withdrawal sleep seen in the flurazepam patients reflected the differing rate of elimination for each patient of N-desalkylflurazepam. They suggested that when the level fell below 60% of maximum level, a rebound would occur. No significant correlation was found between plasma N-desalkylflurazepam levels and sleep variables

during treatment or during withdrawal in this reanalysis. The percent of N-desalkylflurazepam still remaining in plasma after five withdrawal nights was not related to any measures of sleep quality. Thus, in these patients, the type and timing of sleep problems experienced during withdrawal by some flurazepam patients were not related to N-desalkylflurazepam plasma levels. The role and importance of N-desalkylflurazepam are yet to be determined. Further, the relationship of plasma levels to presence in the brain and to action at specific receptor sites is not clearly understood.

It is highly unlikely that the linear relationship sought by most researchers will be found. Mitler et al.<sup>1</sup> thought a curvilinear relationship was suggested by their data. This reanalysis did not support nor did it disprove this possibility. Applying a concept of threshold level may be informative. With this approach, one would maintain that after a minimal level, which may vary from patient to patient, additional increases in plasma level are relatively unrelated to efficacy or daytime drug effects. Greenblatt et al.<sup>11</sup> recently noted that following single doses, volume of distribution of a benzodiazepine appears to be the major determinant of duration of action. These authors, however, felt that elimination half-life was a factor for ultra short half-life drugs and during multiple doses of other benzodiazepines. There are two factors, however, that limit the probability of finding a significant correlation of plasma levels over individuals. One is the marked individual differences in response to similar plasma levels. Another is the problem of tolerance or a plateauing effect<sup>12</sup>. An individual may quickly reach a plateau with respect to improvement in sleep or change in performance which may not vary over several nights of additional drug administration or, which in time, may diminish even though there is an increase in N-desalkylflurazepam plasma level.

Daytime Performance: Neither the data published by Mitler et al.<sup>1</sup> nor the results of this reanalysis have modified the conclusions of Johnson and Chernik<sup>13</sup> that, when compared to a placebo group, no sedative-hypnotic has led to a statistically significant improvement in daytime performance. However, when the pattern of decrement was reexamined, the results indicated a difference between the two hypnotics used in this study. Compared to their own pretreatment mean values, 30 mg of flurazepam was more likely to result in performance below baseline measures than

was 0.5 mg of triazolam. But during treatment there were no statistically significant differences between groups in daytime performance.

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on any of the sleep variables and showed greater night to night variability. Triazolam patients showed a marked increase in sleep latency during the first two withdrawal nights. For these patients, however, there was no rebound in awake time after sleep onset. The flurazepam patients' withdrawal sleep was not statistically different from the placebo group or from their own baseline. In contrast to triazolam patients, flurazepam patients' poor sleep, when present, occurred throughout the withdrawal period with no clustering on one or more nights. There was no clear relationship between plasma N-desalkylflurazepam level during treatment or elimination rate during withdrawal to sleep measures.

These findings are consistent with reports which state that after chronic benzodiazepine use, hypnotic patients may experience one or two nights of poor sleep when treatment is discontinued. For short half-life drugs poorer sleep, if present, occurs on the first withdrawal nights, but for hypnotics with long half-lives poor sleep, if present, may occur any time during the following two-week period. Reanalysis of the pattern of daytime results indicated that performance of flurazepam patients was most affected.

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